Health Equity and Disparities in Breast Cancer Genetics

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Director, International Center for the Study of Breast Cancer Subtypes
Adjunct Professor of Surgery, M.D. Anderson Cancer Center
I have no disclosures
**Socioeconomic Disparities**

<table>
<thead>
<tr>
<th></th>
<th>White Americans</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion Living Below Poverty Level</td>
<td>11.60%</td>
<td>25.80%</td>
</tr>
<tr>
<td>Proportion Uninsured</td>
<td>8.20%</td>
<td>11.90%</td>
</tr>
<tr>
<td>Proportion Unemployed, Age &gt;19 Years</td>
<td>3.30%</td>
<td>6.50%</td>
</tr>
</tbody>
</table>

Sources: U.S. Census Bureau 2013
National Center for Health Statistics/DHHS 2015
US Department of Labor Statistics 2017

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Breast Cancer Burden of African Americans

- Higher mortality
- Advanced stage distribution
  - Younger age distribution
  - Increased risk of adverse tumor features
  - Higher incidence of male breast cancer
- Socioeconomic Disparities
  - Tumor biology
  - Genetics
  - Lifestyle & Reproductive Experiences
  - Environmental exposures
  - Diet/Nutrition

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Disentangling Race and SES

Meta-analysis of breast cancer survival adjusted for SES
AA Mortality Hazard: 1.28 (95% CI 1.18-1.38)
Newman et al, JCO 2006

Pooled analysis of SWOG adjuvant therapy trials:
Equal outcomes for all cancers (regardless of race/ethnicity) except for African Americans with hormonally-driven cancers (breast & prostate cancers)
Albain et al, JNCI 2009

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Mortality</th>
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<tr>
<td>Pre-menopausal</td>
<td>1.39</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>(1.12-1.73)</td>
<td>(1.10-1.82)</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>1.45</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>(1.27-1.66)</td>
<td>(1.28-1.73)</td>
</tr>
</tbody>
</table>
Breast Cancer Burden of African Americans

- Higher mortality
- Advanced stage distribution

- Younger age distribution
  30-40% AA <50; 20% WA <50

- Increased risk of adverse tumor features
  Two-fold higher rates TNBC in AA vs WA

- Higher incidence male breast cancer

- Socioeconomic Disparities
- Delivery of Care
- Tumor biology
- Genetics
- Lifestyle & Reproductive Experiences
- Environmental exposures
- Diet/Nutrition

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Surveillance, Epidemiology and End Results Program; Cancer.gov

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Surveillance, Epidemiology and End Results Program; Cancer.gov

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Disparities in Breast Tumor Biology: ER-Negative Breast Cancer in the U.S.

Li et al; SEER Data, 1992-98
Arch Int Med 2003
SOCIOECONOMIC DISPARITIES

- **Proportion Living Below Poverty Level**
  - White Americans: 11.60%
  - African Americans: 25.80%
  - Hispanic/Latino Americans: 23.20%

- **Proportion Uninsured**
  - White Americans: 8.20%
  - African Americans: 11.90%
  - Hispanic/Latino Americans: 6.50%

- **Proportion Unemployed, Age >19 Years**
  - White Americans: 3.30%
  - African Americans: 6.50%
  - Hispanic/Latino Americans: 4.30%

Sources: U.S. Census Bureau 2013
National Center for Health Statistics/DHHS 2015
US Department of Labor Statistics 2017

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“Breast cancer statistics, 2015: Convergence of incidence rates between black and white women”

CA: A Cancer Journal for Clinicians
29 OCT 2015

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“Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state”
Increased Prevalence of TNBC Among AA Patients Regardless of Age or Stage at Diagnosis

TNBC more common in young women, and in AA women in all age categories.

TNBC more common with more advanced stages, and in AA women at all stages of disease.
Clinical Relevance of Triple Negative Breast Cancer

- Inherently more aggressive pattern of breast cancer
- Fewer systemic therapy options for TNBC: no available targeted therapies
- More common in African American women and in families with hereditary cancer susceptibility (BRCA 1)
Breast Cancer Subtypes

Sorlie T PNAS 2003;100:8418

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Intrinsic Subtypes Heterogeneous

Prat & Perou Mol Oncol 2011;5

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Breast Cancer Survival Among African American Patients by Phenotype

SEER Program, AA pts Dx’d 2010-12 (n=19,836; 20% TNBC)

Akinyemiju et al, Br CA Res Tr 2015
"Breast cancer precursors revisited: molecular features & progression pathways"

Reis-Filho J et al; Histopathology 2010

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Henry Ford Health System
Benign Breast Disease Cohort

• Henry Ford Health System
  – Metropolitan Detroit
  – Approximately 30% African American patients

• Benign Breast Disease Cohort
  – female patients with benign breast biopsy
  – 1994-2005
  – Age 40-70 years
  – 2,588 African Americans
  – 3,566 White Americans

Newman et al, JAMA Onc 2016
Subsequent Breast Cancers

- 106 AA (4.1%) vs. 144 WA (4.0%); p = 0.363
- Mean time to breast cancer diagnosis
  - AA: 6.8 years vs. WA: 6.1 years (p = 0.188)
- Stage Distribution
  - AA: 28% DCIS vs WA: 22% DCIS (p = 0.146)
  - No significant differences in stage distribution for invasive cancers

<table>
<thead>
<tr>
<th>Subtype</th>
<th>AA (%)</th>
<th>WA (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+ and/or PR+, HER2-</td>
<td>63.1%</td>
<td>71.3%</td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+, HER2+</td>
<td>7.7%</td>
<td>11.7%</td>
<td>0.0300</td>
</tr>
<tr>
<td>ER- /PR- and HER2+</td>
<td>4.6%</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>ER-/PR- and HER2- (TNBC)</td>
<td>24.6%</td>
<td>7.4%</td>
<td></td>
</tr>
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</table>
Henry Ford Health System
Benign Breast Disease Cohort: TNBC Incidence

Newman et al JAMA ONC, Dec 2016

African Americans
N=2,588

White/Caucasian Americans
N=3,566

logrank p = 0.0042

Years After Biopsy
Do Outcome Disparities Between AA and WA Pts Persist After Phenotype/Genotype Stratification?

Clinical Trials Data: Sparano et al, JNCI 2012 (ECOG/SWOG/CALGB/NCCTG):
ER-pos: 5-yr DFS worse for AA compared to WA
ER-neg and TNBC: No outcome differences for AA vs WA

Mortality risk higher for AA compared to WA cases of Stage I non-TNBC

US Cancer Centers: Warner et al JCO 2015 (NCCN)
ER/PR-pos and HER2-neg: Mortality risk higher for AA compared to WA
TNBC and HER2-overexpressing: No outcome differences for AA vs WA

Regional: Kroenke et al Br CA Res Tr 2014 (Kaiser and Utah Cancer Registry)
Luminal A: Recurrence risk numerically higher for AA compared to WA
Basal: No outcome differences for AA vs WA

Regional Population-Based Cohort Rauscher et al, Br CA Res Tr 2017 (Chicago):

![Graphs showing survival rates for ER-positive and ER-negative cases, with p-values for comparison.

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Excess risk of death in black versus white women 18 to 64 years of age diagnosed with early-stage breast cancer, by hormone receptor status in sequentially matched patients. Early stage: AJCC stages I to III; demographics: age and census division of residence (group of states) at the time of diagnosis and year of diagnosis; tumor characteristics: stage, tumor size, and grade; treatment: surgery, radiation, chemotherapy, and endocrine therapy; Cases diagnosed between 2004 and 2013, and were observed through December 31, 2014, as compiled in the National Cancer Data Base.

Jemal et al, JCO 2017
TNBC Heterogeneity: TNBC Subtypes

- Vanderbilt University (Pietenpol; Lehmann)
- Gene expression profiles; 21 breast CA datasets
  - >3,000 cases, including 587 TNBC (18% TNBC)
    - Geographic sources: US (predominately Caucasian cases); UK; Sweden; Germany; Singapore; Netherlands
  - 6 subtypes; varying degrees of stem cell-like vs. Luminal Androgen Receptor (LAR) subtypes
- Predictive value of TNBC subtype (MD Anderson)
  - TNBC subtype associated with response to neoadjCTX
  - LAR subtype with lowest response
- Therapeutic value: anti-androgen therapy in LAR
## Tumor Genomics and Breast Cancer Disparities

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases Studied</th>
<th>Selected Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin 2009</td>
<td>Baltimore, MD 18 AA (72% ER-neg) 17 WA (29% ER-neg)</td>
<td>- Prominent interferon signal in tumors of AA patients&lt;br&gt;- Chemokine ligands 10 and 11 expressed more strongly in AA tumor stroma</td>
</tr>
<tr>
<td>Field 2012</td>
<td>Clinical Breast Care Project 26 AA (38% TNBC) 26 WA (35% TNBC)</td>
<td>- Crystallin beta B2; Lactotransferrin; and L-3-Phosphoserine-phosphatase homologue expressed more strongly in AA patients</td>
</tr>
<tr>
<td>Grunda 2012</td>
<td>Birmingham, AL 11 AA (45% ER-neg) 11 WA (9% ER-neg)</td>
<td>- AA patients more likely to have aberrant G1/S cell-cycle regulatory genes&lt;br&gt;- AA patients more likely to have decreased expression of cell adhesion genes&lt;br&gt;- <strong>AA patients more likely to have low or no expression of ESR1, PGR, ERBB2 and estrogen pathway genes</strong></td>
</tr>
<tr>
<td>Lindner 2013</td>
<td>Yale TNBC Cohort 50 AA 69 WA</td>
<td>- Major transcriptional signature of proliferation found to be upregulated in AA cases&lt;br&gt;- Differential activation of insulin-like growth factor1 &amp; BRCA1 deficiency signature in AA cases&lt;br&gt;- <strong>TNBC subtyping</strong>: AA cases more likely to have basal subtype compared to WA</td>
</tr>
<tr>
<td>Kroenke 2014</td>
<td>Pathways and Life after Cancer Epidemiology 128 AA (30% TNBC) 1,176 WA (11% TNBC)</td>
<td>- <strong>PAM50 subtyping</strong>: increased frequency of basal subtype among AA compared to WA cases (41% versus 17%)</td>
</tr>
<tr>
<td>Study</td>
<td>Cases</td>
<td>Selected Findings</td>
</tr>
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<td>--------------</td>
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</tbody>
</table>
| Stewart 2013 | 53 AA (19% TNBC) 574 WA (12% TNBC) | - More differentially expressed genes between AA and WA patients with each stage of tumor progression  
- Resistin (gene linked to obesity, insulin resistance, and breast cancer) expressed >4x higher in AA cases; but lowest in AA TNBC tumors.  
- Increased p53 and BRCA1 subnetwork components in AA tumors |
| Keenan 2015  | 159 AA (17% TNBC) 711 WA (8% TNBC) | - **PAM50**: increased frequency of basal subtype in AA cases (39% vs 19%); fewer luminal A tumors (17% vs 35%)  
- **TNBC subtyping**: increased frequency basal-like 1 and mesenchymal stem-like tumors in AA vs WA cases; no LAR tumors in the AA cases  
- Increased intratumor heterogeneity in AA vs WA cases |
| Ademuyiwa 2017 | 183 AA (33% TNBC) 764 WA (15% TNBC) | - **PAM50 subtyping**: increased frequency of basal subtype in AA cases (35% vs 16%)  
- Median counts of somatic tumor mutations higher in AA vs WA  
- No significant differences in median mutation counts for AA TNBC vs WA TNBC cases |
| Huo 2017     | 154 AA 776 WA          | - **Ancestry Informative Markers used to define African vs European ancestry pts**  
- **PAM50 subtyping**: more basal subtypes in AA cases (36% vs 15%; p<0.0001)  
- AA cases with more TP53 and fewer PIK3CA mutations compared to WA (52% vs 31%; p=2.5 x10^-5 and 24% vs 36%; p=0.012) |
| Levin 2017   | Breast & Prostate CA    | - Work in progress: Differentially expressed genes in AA breast and prostate cancers |
Breast and prostate cancers harbor common somatic copy number alterations (SCNAs) that consistently differ by race-ethnicity.

In the 6 of 9 overlapping race-differentiated SCNAs, African American tumors have more frequent SCNAs in both prostate and breast cancers.

Matthew L. Freedman et al. PNAS 2006;103:14068-14073

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Breast Cancer and African Ancestry: England and Switzerland

• Bowen et al, British J of Cancer 2008: London
  • 22% among Blacks vs 15% among Whites (overall)
  • 25% among Blacks vs 12% among Whites (<60yrs)

• Copson et al, British J of Cancer 2014: UK POSH Study
  • 26% among Blacks vs 18% among Whites, all ≤40 yo

• Rapiti et al, Cancer Medicine 2016: Switzerland

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>Odds Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Switzerland</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>European</td>
<td>1.22 (0.87-1.69)</td>
</tr>
<tr>
<td><strong>African</strong></td>
<td><strong>2.52 (1.44-4.42)</strong></td>
</tr>
<tr>
<td>North American</td>
<td>2.18 (0.83-5.73)</td>
</tr>
<tr>
<td>Central/South American</td>
<td>2.15 (1.07-4.34)</td>
</tr>
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</table>

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Breast Cancer Phenotypes in Brazil, 
(Carvalho et al BMC Women’s Health 2014) 

Highest frequency of TNBC (20%) in northern regions characterized by more west African heritage
Beyond TNBC: AR and ALDH1 in African Ancestry Populations

<table>
<thead>
<tr>
<th></th>
<th>WA</th>
<th>Ethiopians</th>
<th>AA</th>
<th>Ghanaians</th>
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</thead>
<tbody>
<tr>
<td>TNBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadruple Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALDH1-Pos</td>
<td></td>
<td></td>
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</tbody>
</table>

Ongoing Research:
- TNBC subtyping: 200 prospectively-acquired AA, WA, Ethiopian & Ghanaian cases
- TILs and targetable biomarker expression in this cohort

Jiagge, Newman et al, ASCO 2017

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Biologic Plausibility: African Diaspora/
Patterns of Forced Population Migration
Breast Cancer Phenotypes and East/West African Ancestry in USA

- Jemal A and Fedewa S, 

- SEER Registry, 1996-2008

- Frequency of ER-negative breast cancer
  - 183,777 White American patients: 21%
  - 24,639 African American patients: 39%
  - 143 *West African-born* patients: 40%
  - 186 *East African-born* patients: 22%
TNBC and Hereditary Susceptibility

- Prevalence of TNBC in BRCA1-cancers: 50-90%
- Prevalence of BRCA mutations in TNBC: 8-40%
- Greenup et al, Ann Surg Onc 2013
  - 469 TNBC cases: 31% with BRCA1 mutation
    - AA: 20%; WA: 33%; Asian: 29%; Hispanic: 20%
    - Age <40: 44%; 40-49: 27%; 50-59: 25%; 60-69: 13%
- Kwon et al, JCO 2010
  - BRCA testing cost efficient for TNBC pts <50 years
- NCCN Guidelines
  - Genetic counseling for TNBC pts < 60 years
**Germline Genetics and Breast Cancer Disparities**

1997- present: at least 27 studies of BRCA testing in AA patients

- Earliest studies revealing more VUS in AA pts
- More recent studies revealing increased rates of deleterious mutations
- BRCA founder mutations identified in Afro-Caribbean populations of Florida

2017 JAMA Surgery:

- Amankwaa-Frempong, Newman et al- BRCA mutations in 2/3 Ghanaian TNBC cases
Impact of 2011 NCCN Guidelines: HFHS

• 2011: NCCN algorithm advises that all TNBC pts up to age 60 years be referred for genetic counseling, regardless of family history

• HFHS management of TNBC pts ≤60 yrs pre-2011:
  – 52% of WA pts referred for genetic counseling
    • (54% of tested pts found to have mutation)
  – 26% of AA pts referred for genetic counseling
    • (0% of tested pts found to have mutation)

• HFHS management of TNBC pts ≤60 yrs post-2011:
  – 53% of WA pts referred for genetic counseling
    • (15% of tested pts found to have mutation)
  – 50% of AA pts referred for genetic counseling
    • (17% of tested pts found to have mutation)
Ancestry Informative Markers (AIMs): genotyping to quantify geographically-defined heritage

- Native American AIMs associated with reduced breast cancer incidence in Hispanic/Latina Americans
  - Fejerman et al, Nature Communications 2014
  - Fejerman et al, Hum Molec Genetics 2012
  - Hines et al, CA Epi Biomarkers Prev 2016

- African AIMs associated with increased TNBC risk in AA
  Breast cancer Epidemiology and Risk Consortium; AMBER Consortium; Black Women’s Health Study
  - Haddad et al, Carcinogenesis 2016
  - Palmer et al, Cancer Epi Bio Prev 2013
Breast cancer is a heterogeneous disease

- Subtypes vary in treatment needs and prognosis
- Subtypes vary in genetic risk
- Subtypes vary in prevalence by population subset

Eliminating breast cancer is dependent upon our ability to understand and define its diverse nature

- Obligation to study to diverse populations worldwide

ICS BCS Mission: To reduce the global breast cancer burden through advances in research and delivery of care to diverse populations worldwide
International Breast Cancer Research
Eliminating the Threat of Breast Cancer Worldwide

International Collaborations:
• Opportunities to study variations in high-risk patterns of disease
• Opportunities to improve the standard of health care in medically-underserved populations
• Opportunities to cultural and academic exchange
• Opportunities to forge powerful friendships

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Dr. Michael Ohene-Yeboah
Dr. Emmanuel Amankwaa-Frempong
Patients of the Komfo Anokye Teaching Hospital

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Dr. Abebe Engida
Dr. Bekele Mahteme
Dr. Abebe Zerihun
Patients of the St. Paul’s Millenium Teaching Hospital

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Dr. Jessica Bensenhaver
Dr. Erica Proctor
Dr. David Nathanson
Dr. Dhanitale Chitale
Barbara Salem
Dr. Azadeh Stark

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Survival Rates

- 60%
- 43%
- 20%
## R.M.S. TITANIC

<table>
<thead>
<tr>
<th>Passenger Status</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Class</td>
<td>60%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Class</td>
<td>43%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Class</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Outcome is dependent on access to care**

"Of all the forms of injustice, inequality in health care is the most shocking and inhumane"

*Rev. Dr. Martin Luther King, Jr.*
THANK YOU!!!!!!